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E D I T O R I A L

PHARMACY'S PLACE IN CIVIL DEFENSE

THE intensive effort now being directed toward building an effective civil defense organization must of necessity dwarf those preparations made during the early days of World War II. While all responsible people still hope that some means may be found to avert total war, we cannot permit our preference for peace to prevent an all out effort to be prepared should war come.

In the last war, damage to the continental United States was almost negligible—small acts of sabotage and a few forest fires on the West Coast. Most of the civilian defense effort was directed toward blackout precautions and an airplane spotting and reporting organization. Neither of these seem quite as important today since high altitude flying and jet propulsion make the human eye almost meaningless. Radar can "see cities" at night in total darkness and only radar can spot enemy planes soon enough to provide time for defense measures.

The challenge which must be met this time is that of preparing for atomic blast casualties. This alone is a huge task and one for which the United States with its highly vulnerable large cities is poorly prepared. While we may expect the military to offer considerable air protection for our cities it would be sheer folly for us to believe that no enemy could succeed in placing several atomic bombs where they would do great damage. In the first place they need not be flown in by air and for all we know it may be possible to launch them from submarines operating off the coast. The only reasonable course for us to follow is to prepare for the worst.

The key problems that must be met are these:

I—To develop an organization capable of handling some reasonable proportion of the casualties who have some chance of survival.

II—To prepare underground bomb shelters strategically located.

III—To develop an organization trained in detecting and plotting areas containing dangerous levels of radioactivity.

IV—To train workers in the exceedingly tedious and dangerous work of decontamination.

V—To plan for the mass migration, if necessary, of large urban populations.

It is in the first of these projects as listed that pharmacy could and should become an important part. The medical profession alone would be entirely incapable of handling the casualties which would result if a city of a million or more inhabitants were subjected to an atomic disaster. Thousands of casualties suffering with severe burns and shock could be saved only by prompt treatment. It is obvious that with the present ratio of physicians to the general population their services would be pitifully inadequate. Furthermore, many physicians themselves would be casualties and require treatment.

Pharmacies by reason of their strategic locations are ideally suited as places to stockpile and distribute emergency drugs and supplies but this in itself is not enough. The critical need will be for persons trained in the treatment of shock by the use of intravenous therapy and the treatment of extensive burns. To date it is apparent that the need for such personnel has been grossly underestimated. Pharmacists, nurses, dentists and veterinarians—all have a background of college training making them an ideal group for such instruction. The army has had considerable success in training laymen with some medical or pharmaceutical background in these technics and it can be done in civilian defense as well. It must be done without delay and without equivocation. The medical profession must assume the responsibility of training such a corps of workers for it requires experts to act as teachers. It is possible that the medical profession may balk at surrendering certain of its prerogatives to laymen but the emergency demands nothing less.

If a disaster arises and we do not have a large trained corps of such people it will be the responsibility of the medical profession and one which may cause great public resentment and indignation. Physicians have been subjected to criticism in the past with the allegation that public welfare is not their chief concern. Most of this criticism has been unjustified and it has stemmed from those interested in the further socialization of our government. Here is an opportunity for the medical profession to seize the initiative and prove that it is ready and willing to render an outstanding public service.

Pharmacy is ready to do its part. We want to render every bit of this service that we can but we need the guidance, training and direction of the medical profession. Shall we indeed be a part of a great team prepared for any emergency or shall distrust and jealousy prevent it? The answer lies largely with the medical profession. Its future and the lives of many Americans may well reside in the answer.

L. F. Tice

SOME FACTORS RESPONSIBLE FOR IRREGULAR RESULTS WHEN TESTING QUATERNARY AMMONIUM COMPOUNDS.*

By Louis Gershenfeld † and Russell E. Brillhart ††

THE varying results obtained with quaternary ammonium salts when tested by the Food and Drug Administration technique is well known to laboratory workers familiar with these compounds. Such variations are observed not only when comparing results with different laboratories but with workers in the same laboratory, and even with the same worker performing tests at different occasions on the same sample. These inconsistencies have been attributed to different factors (1, 3, 5, 6, 8).

Purpose

This study was an attempt to find some of the possible factors that may cause or play a role in the irregular findings occurring when testing quaternary compounds by the F. D. A. technique to determine their disinfectant efficiency.

Experimental Procedure

The investigations and modifications presented here are varied in type. In each instance control tests were run at frequent intervals using the Food and Drug Administration method of testing (7).

The preparation of glassware, media, and the test organisms was controlled as carefully as possible so as to avoid unusual and usual variations possible from these sources (2).

The glassware used throughout these experiments was prepared in the following manner unless otherwise specified:

1. Washed with ivory soap and tap water.
2. Rinsed three times in tap water.

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* This work was supported by a Fellowship Grant from the Bacteriological Research Laboratories of the Wm. S. Merrell Co., Cincinnati, Ohio.

† Department of Bacteriology, Philadelphia College of Pharmacy and Science.

†† Department of Pharmacology, Rhode Island College of Pharmacy and Allied Sciences.

3. Immersed completely for ten minutes in cleansing solution of the following composition:

   45 grams sodium dichromate
   473 ml. sulfuric acid N. F.
   1500 ml. distilled water.

4. Removed from cleaning solution and drained.
5. Rinsed three times in tap water, using different containers each time.
6. Rinsed four times by immersion in different containers with distilled water.
7. Drained until dry and wrapped in paper.
8. Sterilized in hot air oven at 180° C. for two hours.

F. D. A. medium was used throughout the tests (2) and *Staphylococcus aureus* No. 209 was used as the test organism. Culture age and transfers were controlled carefully at all times following the F. D. A. method (2). Organisms were grown daily in several test tubes and pooled before use in tests, to obviate to some extent errors and variations. All cultures were incubated at 37°C. for 48 hours. Tests were run at 37°C. using a constant temperature bath. Resistance of the organisms was checked daily using standardized phenol solutions. Cetylpyridinium chloride, a quaternary ammonium salt, was the compound employed in the tests. A research sample of 99.8% purity was used in preparing the various dilutions for the tests. This compound was found to exert a killing effect in ten minutes at 1:65,000 dilution following the F. D. A. procedure with broth tubes but growth resulted occasionally where no growth was to be expected. This latter growth was the so-called "skip" result.

All broth transfer tubes showing questionable growth were checked by preparing smears for microscopic examination.

Experiment I

Effects of Varied Rinsing Procedures for the Preparation of Seeding Tubes

Glass seeding tubes were prepared for F. D. A. tests according to the plan outlined previously for all glassware up to the point of wrapping.

Seeding tubes were rinsed individually beforehand according to one or another of the treatments listed below. Following a particular treatment the tubes were drained, dried, wrapped in paper and sterilized at 180° C. for two hours in a hot air oven. After each particular treatment a series of F. D. A. tests were conducted, using only the seeding tubes prepared by and for that treatment. This procedure was followed for the thirteen different treatments.

An aqueous solution of cetylpyridinium chloride was used as the test compound in dilutions of 1:40,000; 1:50,000; 1:60,000 and 1:70,000. These dilutions were found to be the normal ranges for the control tests in the usual F. D. A. method with 1:65,000 the average killing dilution in ten minutes.

Seeding Tube Treatments

1. Rinsed with 1:1000 aqueous solution of cetylpyridinium chloride.
2. Rinsed with 1:1000 aqueous solution of cetylpyridinium chloride followed by two thorough rinses with distilled water.
3. Rinsed with G. L. X. (Wyandotte), an anionic agent, followed with one distilled water rinse. (G. L. X. = 1 teaspoonful per gallon of tap water.)
4. Rinsed with G. L. X. (Wyandotte) followed by a tap water rinse three times and distilled water four times. (G. L. X. = 1 teaspoonful per gallon of tap water.)
5. Rinsed with Neo Suds (Wyandotte), 40% anionic wetting agent, followed with one distilled water rinse. (Neo Suds = 2 teaspoonfuls per gallon of tap water.)
6. Washed tubes with Ivory soap, rinsed three times with tap water and four times with distilled water.
7. Rinsed tubes with isotonic sodium chloride solution.
8. Rinsed tubes with 1:10,000 aqueous solution of cetylpyridinium chloride followed by two rinses with distilled water.
9. Rinsed tubes with 1:20,000 aqueous solution of cetylpyridinium chloride followed by two rinses with distilled water.
10. Rinsed tubes with 1:30,000 aqueous solution of cetylpyridinium chloride followed by two rinses with distilled water.

A further check upon rinsing procedures was carried out by reversing the usual F. D. A. step of adding an aqueous solution of cetylpyridinium chloride followed by a culture of organisms into the seeding tubes to a procedure of adding the 0.5 ml. of organisms first to the seeding tubes followed by the 5 ml. aqueous solution of cetylpyridinium chloride.

The preparation of the seeding tubes for this reversed procedure was:

11. Rinsed tubes with 1:10,000 aqueous solution of cetylpyridinium chloride followed by two rinses with distilled water.
12. Rinsed tubes with 1:20,000 aqueous solution of cetylpyridinium chloride followed by two rinses with distilled water.
13. Rinsed tubes with 1:30,000 aqueous solution of cetylpyridinium chloride followed by two rinses with distilled water.

The findings are recorded in Figure I.

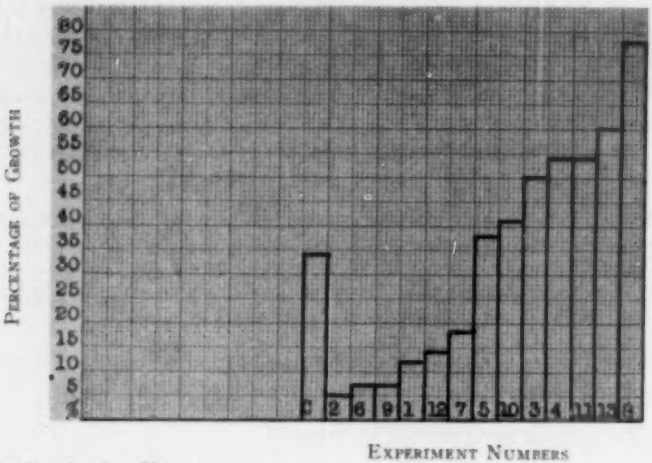
Findings and Discussion

Experiment I

The experimental results shown in Figure I are based upon the different types of rinsings designated, and the corresponding results compared with the control tests. The control tests were used as the basis for comparison because no special rinsing methods were used on those seeding tubes. The control test produced killing effects on the organisms with a 1:65,000 dilution of aqueous cetylpyridinium chloride. Dilutions of 1:40,000; 1:50,000; 1:60,000 and 1:70,000 of the antibacterial agent were used since this rinse was found experimentally to be the most satisfactory covering the rinsing experiments. All tests for a particular dilution were run in quadruplicate with transfers made from seeding tubes to sterile broth tubes at 5, 10 and 15 minute intervals. With the range of four dilutions enumerated previously, 48 sterile broth tubes were used for each rinsing experiment.

The results as obtained in rinsing experiments 1 and 2 indicated that a concentration of 1:1000 cetylpyridinium chloride rinse, even when followed by several distilled water rinses, did produce a residue

FIG. 1—RESULTS OF RINSING SEEDING TUBES UNDER CONDITIONS LISTED BELOW



Explanation for Chart:

Percentage = Percentage of broth tubes showing growth in each experiment according to the F. D. A. disinfectant testing procedure. Each test was run in quadruplicate for each dilution using 1:40,000; 1:50,000; 1:60,000 and 1:70,000 aqueous dilutions of cetylpyridinium chloride. Each experiment required a total of 48 sterile broth tubes and shows the percentage of growth obtained for that experiment as compared with every other experiment including the control under the same test conditions.

Rinsing experiment numbers showing the treatment given seeding tubes before tests:

C = Control.

1 — 1:1000 aqueous solution of cetylpyridinium choride.

2 — 1:1000 aqueous solution of cetylpyridinium chloride followed by 2 thorough rinses with distilled water.

3 — G. L. X. (Wyandotte), an anionic agent, followed with 1 distilled water rinse. (G. L. X. = 1 tsp. per gal. of tap water)

4 — G. L. X. (Wyandotte) followed by a tap water rinse 3 times and distilled water 4 times. (G. L. X. = 1 tsp. per gal. of tap water)

5 — Neo Suds, (Wyndotte) 40% anionic wetting agent, followed with 1 distilled water rinse. (Neo Suds = 2 tsp. per gal. of tap water)

6 — Washed tubes with Ivory soap, rinsed 3 times with tap water and 4 times with distilled water.

7 — Isotonic sodium chloride solution.

8 — 1:10,000 aqueous solution of cetylpyridinium chloride followed by 2 rinses with distilled water.

9 — 1:20,000 aqueous solution of cetylpyridinium chloride followed by 2 rinses with distilled water.

10 — 1:30,000 aqueous solution of cetylpyridinium chloride followed by 2 rinses with distilled water.

11 — 1:10,000 aqueous solution of cetylpyridinium chloride followed by 2 rinses with distilled water.

12 — 1:20,000 aqueous solution of cetylpyridinium chloride followed by 2 rinses with distilled water.

13 — 1:30,000 aqueous solution of cetylpyridinium chloride followed by 2 rinses with distilled water.

on the seeding tube wall. This residue in turn killed most of the test organisms so that very few broth tubes showed growth in contrast to the control.

Rinsing experiments 3, 4 and 5 using G. L. X. and Neo Suds, anionic agents, produced a higher percentage of tubes showing growth than did the control. This in all probability was due to the neutralization occurring between cationic and anionic agents. The residues of G. L. X. and Neo Suds remaining on the seeding tube walls neutralized to some extent the various dilutions of cetylpyridinium chloride. This neutralization or inactivation permitted a higher percentage of broth tubes to show growth in the test as compared with the control.

Rinsing experiments 6 and 7 resulted in few broth tubes showing growth. The results with soap and isotonic sodium chloride solution rinses (rinsing experiments 6 and 7) are difficult to explain, although it is known that the addition of an electrolyte to the solution of a surface active agent alters the surface properties of that solution.

Rinsing experiments 8, 10, 11 and 13, using weaker dilutions of the rinsing substance cetylpyridinium chloride followed by distilled water rinses, resulted in a higher percentage of broth tubes showing growth than for the controls. A number of irregular growths ("skips") were evident too. In rinsing experiments 9 and 12 the number of tubes showing growth was considerably less than the controls. These are irregularities difficult to explain. In experiments 11, 12 and 13 the organisms were added first to the seeding tubes followed by the cetylpyridinium chloride. This reversal of F. D. A. procedure did not change the results. It is interesting to note that experiments 9 and 12 were quite inconsistent with 8, 10, 11 and 13. For some unexplained reason the 1:20,000 dilution used produced entirely different inhibitory results than the 1:10,000 or the 1:30,000 dilutions. This finding was obtained even though the organisms were added first in experiment 12.

During the course of these experiments the usual F. D. A. phenol coefficient tests were carried out concurrently, using phenol dilutions and standard resistance was shown by the organisms. An experiment was performed in quadruplicate using seeding tubes for the phenol tests which were previously rinsed with a 1:1000 aqueous solution of cetylpyridinium chloride. These tests resulted in no

growth occurring in the 5, 10 and 15 minute broth tubes using 1:70, 1:80 and 1:90 dilutions of phenol. The latter findings were in agreement with rinsing experiment 1, using cetylpyridinium chloride. The residue remaining in the seeding tubes killed the organisms irrespective of the phenol dilutions employed in the tests.

In another experiment, daily culture transfers of the organisms were made into tubes prepared as in rinsing experiment 1, using a 1:1000 cetylpyridinium chloride rinse, and also as in rinsing experiment 2, using 1:1000 cetylpyridinium chloride followed by two distilled water rinses. F. D. A. broth was added to these tubes and sterilized. Organisms transferred to the regular daily transfer control tubes grew in the usual numbers after 24-hour incubation at 37° C. while organisms transferred to the 1:1000 rinse treated tubes did not grow. With the 1:1000 rinse treated tubes followed by distilled water rinses, there was some growth but much less than usual. The effects of rinses were again evident in this experiment.

The findings in this group of experiments indicate the possibility that repeatedly used seeding and broth tubes may acquire a residue of the rinsing agent constantly being used. Likewise, if the tubes are washed improperly, there even may be from time to time a residue of the antibacterial compound being tested in the same tubes. Consequently, the need for proper and careful washing and rinsing of all glassware is imperative if accurate results are to be obtained.

Different amounts of residue remaining in seeding and broth tubes might be responsible as one source of the irregular growths or so-called "skips" obtained in the testing of quaternary salts by the F. D. A. procedure and technique. Very small quantities of quaternary salts will affect results readily, while phenol is not so responsive because of its chemical composition and the concentration in which it is used for F. D. A. tests. Anionic and cationic salts may well produce variable results if considered in the light of the above findings.

Experiment II

Effects of Various Sizes of Seeding Containers

The following experiments were conducted so as to note the effects when using varied sizes of seeding tube containers. It was thought this might supply some information concerning the erratic

results obtained when testing quaternary compounds by the F. D. A. technique.

Preparation of glassware, culture media and cultures followed the procedures outlined previously under the general description. Aqueous solutions of cetylpyridinium chloride in concentrations of 1:40,000 and 1:120,000 were used during the course of these tests. The F. D. A. technique and phenol controls were run under the same conditions and in the same sizes of containers as the quaternary compound. All tests were conducted at 37°C.

Seeding tubes 25 mm. x 85 mm. were used for the phenol control and for cetylpyridinium chloride solutions.

The dimensions for the substituted glass tube containers used in each experiment listed were as follows:

Internal diameter	Height	Reference letter used for container
6.00 cm.	7.25 cm.	A
4.50 cm.	5.50 cm.	B
3.50 cm.	8.00 cm.	C
3.75 cm.	8.00 cm.	D
4.75 cm.	8.75 cm.	E

Experiment II (a):

Five ml. of the various aqueous dilutions of cetylpyridinium chloride followed with 0.5 ml. of a *Staphylococcus aureus* culture were placed in each of the containers A, B, C, D and E. Four mm. loop transfers of the medication-bacterial mixture were made from the containers at 5, 10 and 15 minute intervals into 10 ml. quantities of sterile F. D. A. broth. Tests were run in quadruplicate, and broth transplant tubes were incubated at 37° C. for 48 hours.

Phenol controls were made under the same conditions and at dilutions of 1:70, 1:80 and 1:90, using the different sizes of containers.

Experiment II (b):

The same procedure was followed as in experiment II (a), with the exception that 10 ml. quantities of the medication dilutions were placed in each container with 1 ml. of culture of test organisms.

Experiment II (c):

The same procedure was followed as in experiment II (a), with the exception that 0.5 ml. of the culture of test organisms was placed in each of the containers first, followed by 5 ml. of the medication dilutions.

Experiment II (d):

The same procedure was followed as in experiment II (a), with the exception that 1 ml. of the culture of test organisms was placed in each container first, followed by 10 ml. of the medication dilutions.

Frequent tests were run to check the resistance of the test organism, using both phenol and cetylpyridinium chloride.

Findings and Discussion

Experiment II

The results of these experiments have been based on the number of F. D. A. broth tubes showing growth after transfers have been made from the various sizes of seeding containers at 5, 10 and 15 minute intervals following the F. D. A. techniques.

All tests for each dilution of cetylpyridinium chloride were run in quadruplicate. The dilutions found by experiment to be in the most suitable range for the seeding containers used were 1:80,000; 1:90,000; 1:100,000 and 1:110,000 inclusive. Higher and lower dilutions were tried and found unsuitable.

Tests using phenol dilutions of 1:70, 1:80 and 1:90 were run in the various sizes of seeding containers (A, B, C, D and E), and no variation in results was found when compared with the usual seeding tube tests. The resistance of the staphylococcus culture was in the range of 1:80 to 1:85. This was entirely at variance with the results obtained while using cetylpyridinium chloride dilutions. The usual F. D. A. disinfectant tests with cetylpyridinium chloride produced killing effects at a 1:65,000 dilution. The larger seeding containers used in these experiments required higher dilutions of 1:80,000; 1:90,000; 1:100,000 and 1:110,000 of the medicinal agent to fall within readable limits for the five container sizes. The findings in Figures 2 and 3 are based upon these dilutions.

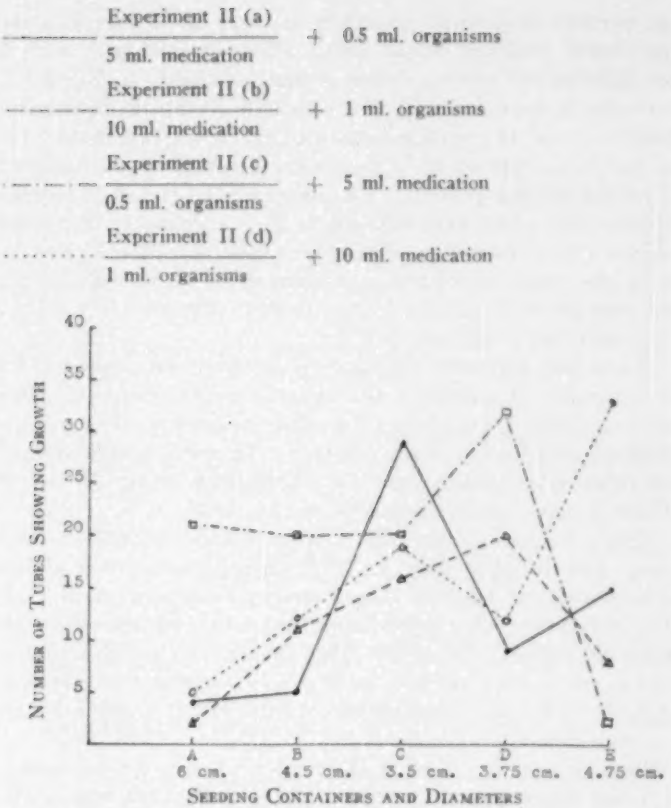


Fig 2—Total number of broth tubes showing growth for each container size following transfers made from each seeding container at 5, 10 and 15 minute intervals. Experimental conditions for the bacterial-medication mixtures used in the seeding containers are indicated above.

Upon inspection of Figure 2, experiment II (a), using 5 ml. of medicament followed by 0.5 ml. of organisms, showed seeding containers A, B and E, the largest diameter containers used in these tests, to have the least number of F. D. A. broth tube transfers showing growth. Seeding containers C and D showed a marked increase

in the number of positive growth tubes over A, B and E sizes. These results indicated better killing effect in containers with a larger diameter and hence a shallower depth of liquid (A, B and E). The results in experiment II (b), in which 10 ml. of medicament followed by 1 ml. of organisms was used, showed approximately the same growth as experiment II (a), with the exception of container C which showed less growth. In experiments II (c) and II (d) the organisms were added first, followed by the medicament. A greater number of growth tubes were obtained in experiment II (c) generally than in the other experiments. Experiment II (d) findings followed experiment II (a) and II (b) results rather closely and were not consistent with experiment II (c).

It was very noticeable that seeding container size C produced a greater number of transfer tubes showing growth than the other containers. Also it was evident that the experiments, using a 5 ml. medicament plus 0.5 ml. of organisms, or vice versa, produced more broth tubes with growth than the experiments using 10 ml. of medicament plus 1 ml. of organisms, or vice versa.

Figure 3 shows the summation of the number of transfer tubes showing growth obtained in the broth tube transfers from all the tests employing the different sizes of seeding containers (A, B, C, D and E). Dilutions of cetylpyridinium chloride used were the same as listed for Figure 2 and all test dilutions were run in quadruplicate. Therefore, 48 transfer broth tubes were used for each container size, i. e., A, B, C, D and E, and for each experiment as listed in Figure 2, i. e., four different experiments.

Thus for example, if all broth transfer tubes used for container size B had shown growth, a total of 192 growth tubes would have been possible instead of the 47 which showed growth. Even though there were numerous indications of bacterial survival, "wild plusses," where there should have been a killing effect in the results of the various dilutions at the different time intervals, the fact was very evident that different numbers of growth tubes occurred while using different sizes of seeding containers. Thus, C and D container sizes permitted a considerably larger number of transfer broth tubes showing growth than did the other sizes, and especially A and B. Also it was noted, as shown in Figure 2, that the 5, 10 and 15 minute transfers were consistent in this same respect, with quadruplicate tests run in all instances.

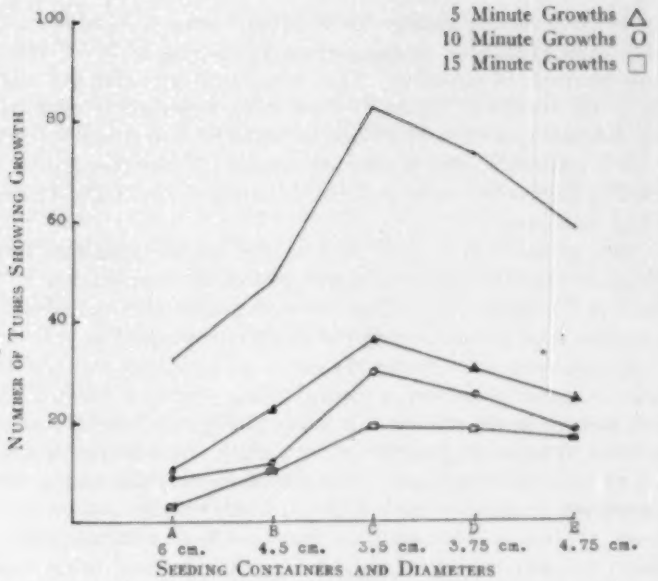


Fig. 3—Upper graph: Total number of all broth tubes showing growth following transfers made from the seeding container sizes listed. The medication-bacterial mixture quantities used are given in experiments II (a), (b), (c) and (d) (Fig. 2).

Lower graphs: Number of broth tubes showing growth under the conditions listed above but graphed for each time interval of 5, 10 and 15 minutes.

Phenol tests using phenol as the medication did not show these differences when using different sizes of containers but were entirely consistent as with the regular seeding tubes. Phenol tests as usual did not show any evidence of "wild plusses" or "skips."

From the results shown in Figures 2 and 3 it was evident that different sizes of seeding containers produced different growth results, as reflected by the number of F. D. A. transfer broth tubes showing growth. Those seeding containers showing the greater diameter (A, B and E) produced a smaller number of growth results, while size C with 3.50 cm. diameter and D with 3.75 cm. diameter showed the largest number of tubes revealing growth. This condition prevailed

very definitely in the findings as noted in Figure 3, whether in the overall total growth or at the various time levels of 5, 10 and 15 minute intervals of sampling. This same result was obtained essentially in the results of Figure 2, wherein the experiments were tried using different quantities of medication-bacterial mixtures and reversing their addition to the seeding containers. These results may be caused by the shallow layer of liquid occurring in the larger diameter seeding containers.

In a surface active agent such as the cationic substance cetylpyridinium chloride there is a higher molecular concentration at the surface of the liquid (4). Thus, we may assume that by increasing the surface area but decreasing the depth of the liquid, as was done in the containers with greater diameters as compared with the two smaller diameter containers, a greater killing effect was exerted upon the organisms in the solution. A study of Figures 2 and 3 supports this point in terms of growth. As the depth of medication-bacterial mixture in containers C and D increased, so was the killing effect lessened and resulted in more F. D. A. broth transfer tubes showing growth. Likewise, this same point may have been a definite factor in causing the dilutions of cetylpyridinium chloride used being necessarily in the 1:80,000-1:110,000 range rather than in the range of 1:40,000-1:80,000, as usually is employed with the regular type of seeding tubes of 25 millimeter diameter or less with a killing effect produced at 1:60,000 to 1:65,000 dilution.

"Wild plusses" and so-called "skips" were evident in these tests, as is customary.

Phenol compounds did not respond in a surface active manner; hence tests in the various sizes of containers did not alter the typical phenol test results as compared with regular seeding test tubes.

It was noted, too, in the experiments shown in Figure 2 that the addition of organisms first as in experiment II (c) produced a much larger number of transfer tubes showing growth as compared with the other experiments. This might be explained by the fact that the organisms have a definite chance to migrate to the glass sidewalls and bottom of the container before addition of the medication. These organisms were in a more protected position and had less chance of being acted upon by the medicament, especially at such high dilutions, and after taking surface concentration of the medication liquid into consideration.

Experiment III

Area Sampling in Seeding Tubes

Medication-bacterial mixture samples were taken from different areas within the seeding tubes at 5, 10 and 15 minute intervals, following the F. D. A. technique. The glass seeding tubes used were 85 mm. in height by 25 mm. in diameter. A 4 mm. inside diameter platinum loop was used for obtaining the samples. The bacterial-medication mixtures used were phenol 1:70, 1:80 and 1:90 and aqueous solutions of cetylpyridinium chloride ranging in dilution from 1:40,000 to 1:120,000 in increments of 10,000 combined with the designated quantities of *Staphylococcus aureus* cuture.

Experiment III (a):

One loopful of medication-bacterial mixture obtained from center of seeding tubes *under surface* of liquid one-half way into depth of liquid without touching tube side wall. Samples were taken at 5, 10 and 15 minute intervals and transferred to test tubes containing 10 ml. each of sterile F. D. A. broth.

Experiment III (b):

One loopful of medication-bacterial mixture obtained from surface of liquid and transferred as in experiment III (a).

Experiment III (c):

One loopful of medication-bacterial mixture obtained after touching *glass bottom in center* of seeding tube and transferred as in experiment III (a).

Experiment III (d):

One loopful obtained after touching *side* of seeding tube one-half way down depth of liquid in the tube and transferred as in experiment III (a).

Experiment III (e):

A group of three F. D. A. tests was conducted for each dilution of medication mixture in which loop samples were obtained from the liquid one-half way down into the depth of the bacterial-medication mixture after first *touching the side* of the tube at that depth.

Concurrently with each of the above experiments, identical series were employed, using the modification of adding the organisms first to the seeding tubes followed by the medication mixture.

Phenol test dilutions of 1:70, 1:80 and 1:90 produced F. D. A. results, using the same modification as listed in the experiments. The resistance of the staphylococcus culture was checked constantly against phenol.

Experiment III (f):

Glass strips 25 mm. by 3 mm. by 1 mm. were inserted in tubes of F. D. A. broth and sterilized. Six tubes of this broth were inoculated with the daily smooth culture of *Stapyhlococcus aureus* and six tubes with a rough culture of *Staphylococcus aureus*. All tubes were incubated at 37°C. for 48 hours and examined for the type and amount of growth.

Findings and Discussion

Experiment III

Experiment III (a) in which loopful samples were taken from the medication-bacterial mixture under the surface of the liquid produced only two broth tubes showing growth, even using a range of 1:40,000 to 1:120,000 dilutions of cetylpyridinium chloride. In experiment III (b) samples taken with the loop merely touching the surface of the liquid produced approximately the same results as the previous experiment. However, in experiment III (c) with loopful samples taken from the bottom of the tubes, growth occurred in six of the corresponding broth tubes. In loopful samples of experiment III (d), in which the loop needle touched the side of the tube while being dipped half way into the depth of the medication-bacterial mixture, there were 18 broth tubes showing growth, as evidenced in Table I.

In experiment III (e) results as shown in Table II, it was found that if organisms were added first to the seeding tubes followed by the medication, side tube samples produced approximately three times as many broth tubes with growth as when the organisms were added last to the medication. Twenty-five broth tubes showed growth at the various time intervals from the side tube samples in which the organisms were added first. Nine tubes showed growth when the organisms were added last to the medication mixture, even though the experiments were done at the same time under the same conditions.

TABLE I

GROWTH RESULTS AFTER OBTAINING TRANSFER SAMPLES FROM DIFFERENT AREAS OF THE SEEDING TUBE WITHIN THE MEDICATION BACTERIAL MIXTURE *

Dilutions of cetyl-pyridinium chloride used in experiments	Under surface of liquid Expt. III (a)	Surface of liquid Expt. III (b)	Bottom of liquid touching tube Expt. III (c)	Side of tube touched 1/2 way in depth of liquid Expt. III (d)
1 : 40,000	0	0	0	0
1 : 50,000	0	1	0	0
1 : 60,000	0	0	0	0
1 : 70,000	1	0	0	2
1 : 80,000	0	0	1	1
1 : 90,000	0	0	4	4
1 :100,000	0	1	0	4
1 :110,000	0	1	1	4
1 :120,000	1	0	0	3
	2	3	6	18

* Figures indicate total number of F. D. A. broth tubes showing growth resulting from above types of sampling transfers. All tests were done in duplicate for each dilution and each method of sampling following the F. D. A. technique except as modified above.

In experiment III (f) sterile glass strips were immersed for 24 hours in broth tubes inoculated with smooth and rough cultures respectively of *Staphylococcus aureus,* with the normal phenolic resistance. Both culture types showed some visible adherence to the glass strips and tube walls in the broth tubes, with the rough organisms producing the most and the larger clumps. The same effect was noted in the daily transfer cultures after incubating 24 hours.

It is definitely evident in the experimental results obtained that samples taken after touching the side or bottom of seeding tubes produced more broth tubes showing growth than samples taken without touching these areas. Modifying the usual F. D. A. technique by adding organisms first to the seeding tubes followed by the medicament served to emphasize this fact.

Upon analysis of the results, it would seem that organisms migrated and adhered to the glass walls of the tubes (3). This condition can possibly be attributed to the positive charged glass being attractive for the negatively charged organisms. When organisms tend to adhere to the glass walls, a highly diluted medicinal substance such as cetylpyridinium chloride has less opportunity of coating the bacterial surface completely. This condition permits better survival for organisms as well as the possibility of erratic and variable results in tests performed. This may account for some of the so-called erratic results. Likewise, in a surface-active substance such as the cationic agent, cetylpyridinium chloride, there is a higher molecular concentration of the substance at the surface of the solution than within the solution, because the molecules of the substance tend to concentrate at the surface (4). This fact may have a tendency to aid in explaining the no-growth results for samples taken at and under the surface, as shown in Table I, even at high dilutions in contrast to the growths attained when the sampling loop touched the sides and bottoms of the seeding tubes.

TABLE II

Results Obtained in F. D. A. Broth Tubes Following Loop Sampling by Touching Side of Seeding Tube Wall One-Half Way Within Depth of Seeding Tube Mixture—Experiment III (e)

Seeding Tube *Side* Samples
Experiment III (e)

Dilutions of cetylpyridinium chloride	Five minutes		Ten minutes		Fifteen minutes	
	A	B	A	B	A	B
1:50,000	+ + −	+ − −	+ − −	− − −	− − +	− − −
1:60,000	+ − +	− − −	− + −	− − −	+ − +	− − −
1:70,000	+ + +	− − −	+ + −	− − −	+ + −	− − −
1:80,000	+ + +	+ + +	+ + +	+ + +	+ + +	+ + −

A = growth results with organisms added first to seeding tubes followed by medication.

B = growth results with medication added first to seeding tubes followed by organisms.

+ denotes growth in broth tubes at time intervals indicated.

When organisms were placed in the seeding tubes first, followed by the medication, an opportunity was afforded the organisms to migrate and adhere to the glass walls before the cetylpyridinium chloride was added. This lessened the chances for full contact with the organisms and perhaps less concentration of the cationic substance in the region of the glass walls as pointed out previously. Table II results bear out these points in the number of broth tubes showing growth.

On the basis of the test results shown, in order to obtain the same killing effect, a stronger concentration of cetylpyridinium chloride seems necessary if organisms were added first to the seeding tubes followed by cetylpyridinium chloride as compared with the opposite procedure of adding the medicament first.

Summary

In experiment I many F. D. A. tests were conducted, using different dilutions of cetylpyridinium chloride, while checking upon the effects of rinsing seeding tubes with various dilutions of cetylpyridinium chloride, as well as using different types of other rinses, i. e., tap water, distilled water, isotonic sodium chloride solution. Tests were tried first using rinses of several anionic agents and their effects noted on cetylpyridinium chloride as a test agent.

The test organism was *Staphylococcus aureus* #209.

The effects of these rinsing substances were checked upon the regular phenol dilutions used in the F. D. A. technique.

In a number of the experiments the F. D. A. procedure of adding medication followed by organisms to the seeding tubes was reversed by adding organisms first followed by medicament.

In experiment II a series of tests were conducted, following the F. D. A. technique for disinfectants with the modification of using seeding containers of five different sizes, and all larger than the usual tubes employed in the F. D. A. tests.

The quantity of medication-bacterial mixture used in the larger seeding containers was kept at the 5.5 ml. quantity in one series of tests but doubled in another group of tests to note the results produced. Also, tests were performed in which the usual procedure of adding bacteria to the medication was reversed.

In experiment III a number of tests were conducted employing the F. D. A. technique in which four mm. loop samples were taken

from various locations within the seeding tubes and transferred to sterile broth tubes, with the object of determining the effect of sampling different areas within the seeding tube.

Evaluations were based upon the number of broth transfer tubes showing growth in each method.

Another group of tests were performed, in which the F. D. A. technique was followed except for the modification of adding organisms first to the seeding tubes followed by the medicament and noting the effect of sampling different areas under these conditions.

Experimental work was performed to show the adherence of smooth and rough organisms to glass.

Conclusions

From experiment I, the following conclusions result when testing the bactericidal efficiency of quaternary compounds by the F. D. A. technique. All glassware and especially seeding tubes used should be washed and rinsed carefully and thoroughly, to obviate possible errors resulting from residues of the substances used being deposited on the tube walls.

Varying amounts of residues remaining on tube walls could be partially responsible for some of the non-reproducible results occurring in the same or different laboratories from time to time when testing quaternary ammonium compounds.

Some of the so-called "skips" and "wild plusses" may be produced to some degree by variable amounts of residues on the tube walls.

Anionic substances used in washing or rinsing procedures for glassware, such as test tubes, may interfere seriously with the accurate testing of cationic substances if the glassware is not rinsed properly.

Phenol is not affected by residues readily; therefore, tests using phenol are reproducible when using the F. D. A. technique as compared with quaternary compounds.

In experiment II, it is to be noted that the diameter of the seeding container influences the number of broth tubes showing growth following the F. D. A. technique when using cetylpyridinium chloride. This change is not evident with phenol.

Doubling the quantity of medication-bacterial mixture in the larger seeding containers produced fewer broth tubes showing growth, as compared with the usual F. D. A. disinfectant test procedure quantity of 5.5 ml.

Seeding containers of larger diameter than the F. D. A. specification required a high dilution of cetylpyridinium chloride in order to obtain the same range of killing effect, as is evidenced when using the regular F. D. A. technique.

In experiment III varied results were obtained with cetylpyridinium chloride in the F. D. A. technique, depending upon the particular area of the seeding tube from which the loopful of medication-bacterial mixture was obtained for transfer to broth tubes.

This error might be lessened by attempting to obtain loop samples from the same area each time.

The practice of adding organisms first followed by the medicament in the seeding tubes produces results different than those obtained in the usual F. D. A. procedure. A greater concentration of cetylpyridinium chloride seems necessary to kill if the organisms are added first to the seeding tubes followed by the medication as compared with the usual addition of medicament followed by the organisms in the F. D. A. procedure.

Phenol samples run under the same conditions did not produce these effects but yielded the results of the usual F. D. A. procedure.

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SELECTED ABSTRACTS

The Effect of Desoxycorticosterone Acetate and Vitamin C on Rheumatoid Arthritis. Mettior, S. R., Gordan, G. S., Rinehart, J. F., Plumhof, C., Ellenhorn, M. J., and McBride, A. *Bull. Univ. Calif. Med. Center 1*:337 (1950). Various and conflicting reports have appeared in recent months as to the effectiveness of the adrenal cortical hormones on rheumatic conditions. The authors contributed to this growing fund of information the results of their trials with desoxycorticosterone acetate combined with vitamin C.

Twenty-five patients with rheumatoid arthritis and 1 patient with rheumatoid arthritis combined with disseminating lupus erythematosus were treated with 5 mg. of desoxycorticosterone acetate intramuscularly followed immediately by 1 Gm. of sodium ascorbate intravenously. The frequency of dosage was every 8 hours for several days for 3 patients, daily for 2 patients, weekly for 14 patients, and twice weekly for the remainder. In order to minimize the effects of suggestion, placebo injections were given occasionally.

The authors reported that all of the patients showed a prompt lessening of pain and tenderness and an increased range of motion in the involved joints following the first injections. Initial benefits were maintained by injections given once or twice a week. Although the optimal dosage schedule has not been determined, the authors felt that there was no advantage to the administration of injections more frequently than twice a week.

The authors also emphasized the necessity for careful observation of weight, blood pressure, and of the presence or absence of edema. In this study some of the patients receiving daily or more frequent doses develop mild salt retention with edema but there were no signs of such side effects if the dosage was 5 mg. once or twice a week. No elevation of blood pressure occurred. This report was presented after two months experience.

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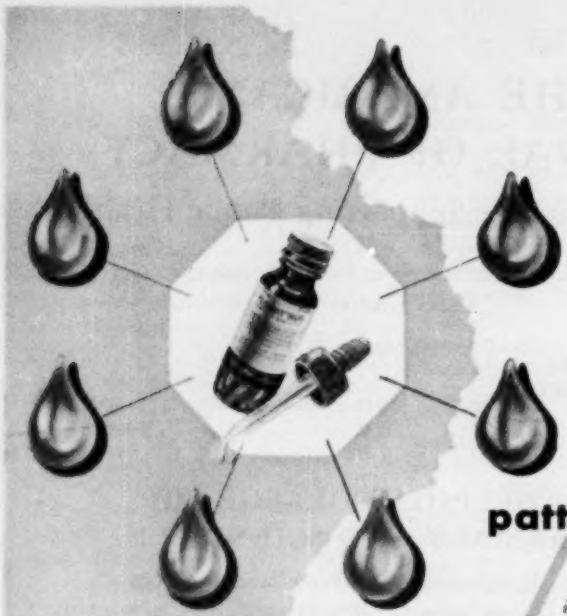

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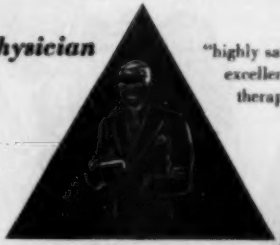

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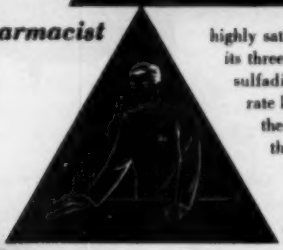

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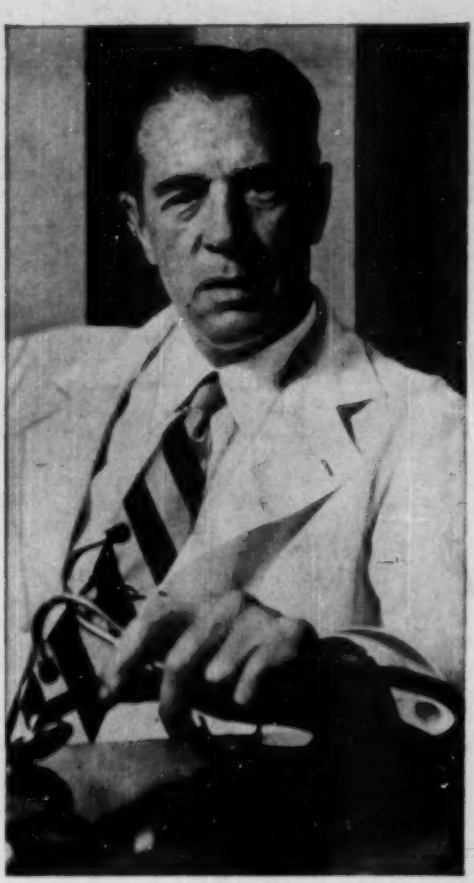

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